PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4-32527A/607		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/08669	05.08.2003	06.08.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K31/55		
Applicant		
NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.02.2004	08.09.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08669

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-8 as originally filed

Claims, Numbers

1-8 filed with telefax on 16.08.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-5, 7,8

   because:

   ☒ the said international application, or the said claims Nos. 1-5,7,8 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	6
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item I

The basis of this written opinion are the following documents:
Pages 1-8 of the description as originally filed and claims 1-8 as sent by fax on 16.08.2004.

Re Item III

The subject-matter of claims 1-5, 7, 8 is related to subject-matter considered to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4) (a) (I) PCT).

Re Item V

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

D1: EP-A-0 751 129 (PORTELA & CA S A) 2 January 1997 (1997-01-02)
D2: EP-A-0 646 374 (CIBA GEIGY AG) 5 April 1995 (1995-04-05)
D3: WO 00/01416 A (BIALER MEIR ;YAGEN BORIS (IL); SINTOV AMNON (IL); VOLOSOV ANDREW () 13 January 2000 (2000-01-13)

1. Novelty

D1 discloses substituted dihydrodibenzo(b,f)azepines for the treatment of some central nervous system disorders. Among the disclosed compounds oxcarbazepine (R1 and R2 together represent an oxy-group), 10-acetoxy-10,11- dihydro-5H-dibenz/b,f/azepine-5-carboxamide and 10-ethoxycarbonyloxy-10,11- dihydro-5H-dibenz/b,f/azepine-5-carboxamide are explicitly disclosed (see column 1, lines 19-22; column 2, lines 38-39 and column 3 lines 42-43).

D2 is directed to the use of oxcarbazepine tablets and the use as an anticonvulsive is explicitly disclosed (see page 2, lines 1-5).

D3 discloses pharmaceutical compositions containing low-melting waxes. Among the pharmacologically active agents 10-hydroxycarbazepine is explicitly mentioned.

The subject-matter underlying claims 1-8 is the treatment of tinnitus or other inner ear/cochlear excitability related diseases.

The subject-matter of claims 1-8 is therefore novel over the cited prior art (Art. 33(2)

PCT).

2. Inventive step

The problem underlying the present application is the provision of pharmaceutical compositions for the treatment of tinnitus and other ear/cochlear excitability related diseases. The solution, according to the applicant lay in the provision of compounds as claimed.

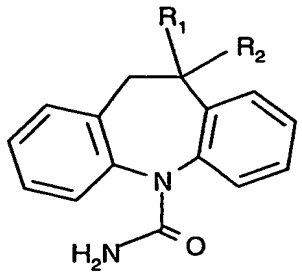
There is no hint in the cited prior art that tinnitus or other ear/cochlear excitability related diseases could be treated with the claimed compounds. However, the applicant should made aware that the application lacks evidence in the form of experimental data that the diseases are treatable by the compounds of formula I.

In the absence of converse data, for the purposes of the international preliminary examination report it is **at present assumed**, that the problem was solved over the whole of the claimed scope.

An inventive step therefore is acknowledged for claims 1-8 (Art. 33(3) PCT).

CLAIMS

1. The use of a compound of formula I



(I)

wherein

(a) R_1 represents hydrogen, and R_2 represents hydroxy or C_1-C_3alkyl carbonyloxy, or

(b) R_1 and R_2 together represent an oxo group,

or pharmaceutically acceptable salts thereof for the treatment of tinnitus or other inner ear/cochlear excitability related diseases.

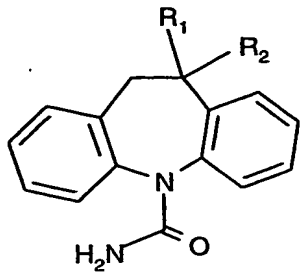
2. The use of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof wherein R_1 and R_2 together represent an oxo group.

3. The use of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof wherein R_1 represents hydrogen, and R_2 represents hydroxy.

4. The use of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof wherein R_1 represents hydrogen and R_2 represents acetoxy.

5. The use of a compound of formula I according to any one of claims 1 to 4 for the treatment of tinnitus.

6. A pharmaceutical composition which incorporates as active agent a compound of formula I



(I)

wherein

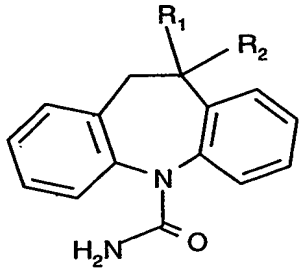
(a) R_1 represents hydrogen, and R_2 represents hydroxy or C_1-C_3alkyl carbonyloxy, or

(b) R_1 and R_2 together represent an oxo group,

or pharmaceutically acceptable salt thereof,

for use in the treatment of tinnitus and other inner ear/cochlear excitability related diseases.

7. The use of a compound of formula I



(I)

wherein

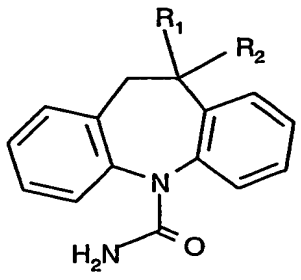
(a) R_1 represents hydrogen, and R_2 represents hydroxy or C_1-C_3alkyl carbonyloxy, or

(b) R_1 and R_2 together represent an oxo group,

or pharmaceutically acceptable salt thereof,

for the manufacture of a pharmaceutical composition for the treatment of tinnitus and other inner ear/cochlear excitability related diseases.

8. A method for the treatment of tinnitus and other inner ear/cochlear excitability related diseases in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I



(I)

wherein

(a) R_1 represents hydrogen, and R_2 represents hydroxy or C_1-C_3alkyl carbonyloxy, or

(b) R_1 and R_2 together represent an oxo group,

or pharmaceutically acceptable salt thereof.

9. The use of a compound of formula I according to claim 1, wherein R_1 represents hydrogen and R_2 represents hydroxy or C_1-C_3alkyl carbonyloxy and wherein the compound is employed in enantiomerically pure form.